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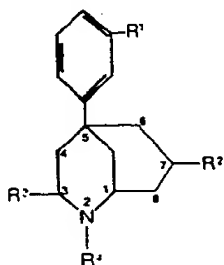
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⑤④ **Phenylmorphans, processes for their preparation, pharmaceutical compositions containing them, and 4-phenyl-tetrahydro-pyridines.**

⑤⑦ A novel 5-phenylmorphan compound having the Formula



VI

wherein:

R¹ is hydrogen, hydroxy or C₁-C₃ alkoxy;
R² and R³ independently are hydrogen, C₁-C₅ alkyl or CH₂C₂-C₆ alkenyl; except that R² and R³ both are not hydrogen;

R⁴ is hydrogen, C₁-C₁₀ alkyl, phenyl C₁-C₃ alkyl, CH₂C₂-C₆ alkenyl, or CH₂C₂-C₆ cycloalkyl; and
the pharmaceutically acceptable acid addition salts thereof are disclosed. These compounds are useful in the treatment of pain.

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PHENYLMORPHANS, INTERMEDIATES AND
METHOD OF PREPARATION

Novel 5-phenylmorphans are useful for their analgesic activity. A process for their preparation from 1,2,5,6-tetrahydro-4-phenyl-pyridines is disclosed.

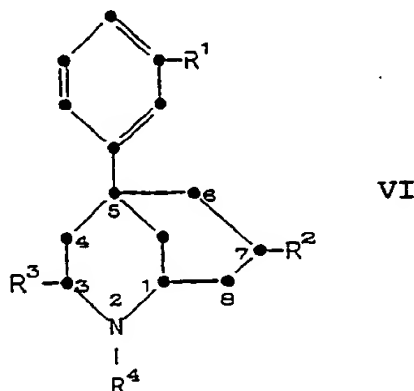
Analgesics are widely used in the treatment of mild pain due to CNS disorders and of more severe pain due to diseases such as cancer. Many of the agents commonly used to relieve instances of severe pain are extremely dangerous due to their potency and to their addicting properties. Morphine is among such analgesic agents, and causes severe physical dependence. Even with such drawback, morphine is extensively used simply because of the non-existence of a more desirable agent. A great deal of research has been devoted, however, to finding compounds capable of alleviating severe pain to the degree accomplished with morphine, but which display little or no physical dependence capacity. Among the more recent discoveries is the series of compounds referred to generally as the "phenylmorphans". May and Murphy reported that racemic 5-(3-hydroxyphenyl)-2-methylmorphan possesses an analgesic potency nearly equivalent to that of morphine, J. Org. Chem., 20, 1197 (1955). May and Takeda later reported that the (-)isomer of 5-(3-hydroxyphenyl)-2-methylmorphan is an analgesic with morphine-like potency but with no physical dependence capacity, J. Med. Chem., 13, 805 (1970).

One of the major difficulties with the early syntheses of this extremely potent series of compounds

was the low overall yields and the difficulty in handling the intermediates. Rogers and May recently reported an improved synthesis of (-)-5-(3-hydroxyphenyl)-2-methylmorphan, but still the overall yield was only one percent, J. Med. Chem., 17, 1328 (1974). A number of novel 5-(3-hydroxyphenyl)-2-(substituted)-morphans have been prepared and evaluated by Ong and co-workers, J. Med. Chem., 17, 133 (1974). None, however, were as potent as the 5-(3-hydroxyphenyl)-2-methylmorphan.

To date, no phenylmorphans having various substituents at positions other than the morphan 2-position have been prepared. The purpose of this invention is to provide certain 5-phenylmorphans having alkyl and alkenyl substituents at the 3 and 7-positions. Another purpose of the invention is to provide an improved synthesis of both new and known phenylmorphans.

This invention provides a 5-phenylmorphan compound having the formula



wherein:

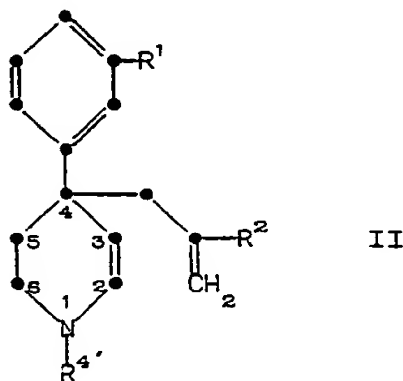
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 and R^3 independently are hydrogen, C_1-C_5
 alkyl or $CH_2C_2-C_4$ alkenyl; except that R^2 and R^3 both
 5 are not hydrogen;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3
 alkyl, $CH_2C_2-C_9$ alkenyl, or $CH_2C_3-C_6$ cycloalkyl; and
 the pharmaceutically acceptable acid addition
 salts thereof.

10 Preferred compounds of the invention are
 those wherein R^1 is hydrogen, hydroxy or methoxy; R^2
 and R^3 independently are hydrogen or $n-C_1-C_5$ alkyl; and
 R^4 is $n-C_1-C_{10}$ alkyl, benzyl, 2-phenethyl, $CH_2C_2-C_3$
 alkenyl and $CH_2C_3-C_4$ cycloalkyl.

15 This invention also provides pharmaceutical
 formulations useful in the treatment of pain comprising
 an analgesically effective amount of a 5-phenylmorphane
 of the above formula VI in combination with a suitable
 pharmaceutical carrier.

20 This invention also provides a 1,4,5,6-tetra-
 hydro-4-phenyl-4-(2-propenyl)-pyridine compound of the
 formula



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wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

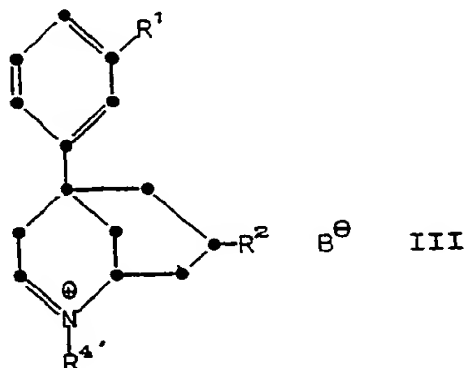
R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl; and

5 $R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl.

The invention also provides a 2,3-dehydro-5-phenylmorphan compound of the formula

10

15



wherein:

20 R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$

alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl; and

25 B^{\ominus} is an anion.

The invention also provides a 3,4-dehydro-5-phenylmorphan compound of the formula

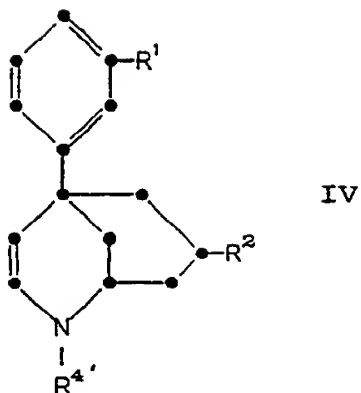
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wherein:

 R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy; R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl; and

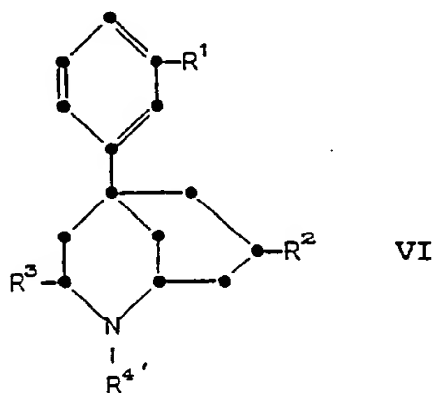
15 $R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or $CH_2C_3-C_6$ cycloalkyl.

The invention also provides a process of preparing a 3-substituted-5-phenylmorphine compound having the formula

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wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;

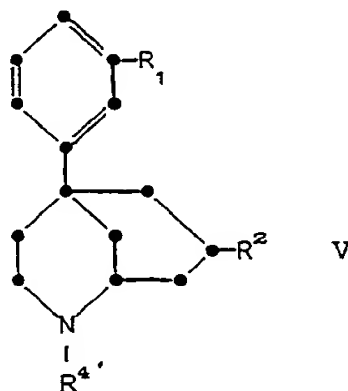
5 R^3 is C_1-C_5 alkyl or $C_2C_2-C_4$ alkenyl;

$R^{4'}$ is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

10 characterized by alkylating the 2,3-dehydro-5-phenylmorphanium salt of formula III wherein R^1 , R^2 and $R^{4'}$ are as above with the compound R^3M where R^3 is as above and M is a cationic radical and recovering as the free base or the pharmaceutically acceptable acid addition salt thereof.

15 The invention also provides a process of preparing a 7-substituted-5-phenylmorphane compound having the formula



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wherein:

- R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 is C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;
 $R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3
 5 alkyl or $CH_2C_3-C_6$ cycloalkyl; and
 the pharmaceutically acceptable acid addition salts thereof

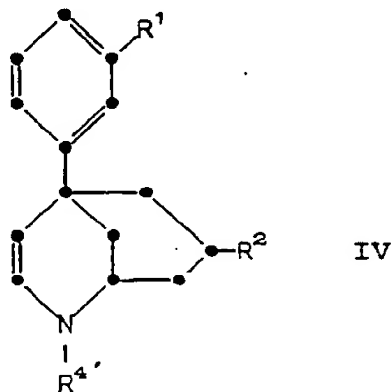
- characterized by reducing the 2,3 dehydro-5-phenylmorphanium salt of formula III wherein R_1 , R_2 and
 10 $R^{4'}$ are as above with a reducing agent and recovering as the free base or the pharmaceutically acid addition salt thereof.

- The invention also provides a process of preparing a 7-substituted-5-phenylmorphan compound
 15 having the above formula V wherein:

- R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 is C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;
 $R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3
 20 alkyl, or $CH_2C_3-C_6$ cycloalkyl; and
 the pharmaceutically acceptable acid addition salts thereof characterized by hydrogenating a 3,4-dehydro-5-phenylmorphan compound of the formula

25

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wherein R^1 , R^2 and $R^{4'}$ are as above and recovering as the free base or as the pharmaceutically acceptable acid addition salt thereof.

5 The invention also provides a process for preparing a 2,3,7-substituted-5-phenylmorphane compound of formula VI wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 and R^3 independently are hydrogen, C_1-C_5
10 alkyl or $CH_2C_2-C_4$ alkenyl; except that R^2 and R^3 both are not hydrogen;
 R^4 is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, $CH_2C_2-C_9$ alkenyl, or $CH_2C_3-C_6$ cycloalkyl; and
the pharmaceutically acceptable acid addition
15 salts thereof

characterized by reacting a 3,7-substituted-5-phenyl-morphane of formula VI wherein R^1 , R^2 and R^3 are as above and $R^{4'}$ is hydrogen with an alkylating or alkenylating agent wherein R^4 is as above other than
20 hydrogen and recovering the free base or the pharmaceutically acceptable salt thereof.

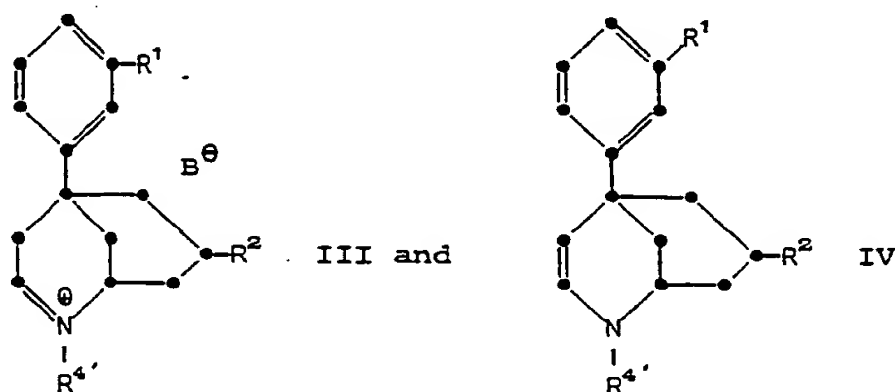
The invention also provides a process for preparing a 5-(3-hydroxy phenyl)morphane compound of formula VI
25 wherein:

R^1 is hydroxy;
 R^2 and R^3 independently are hydrogen, C_1-C_5
alkyl or $CH_2C_2-C_4$ alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl, C_1-C_3 alkyl, $CH_2C_2-C_9$ alkenyl, or $CH_2C_3-C_6$ cycloalkyl; and the pharmaceutically acceptable acid addition salts thereof

characterized by reacting a 5-(3-methoxyphenyl)morphan with an acid such as hydrobromic acid and acetic acid or boron tribromide followed by recovery of the free base or the pharmaceutically acceptable acid addition salt thereof.

This invention also provides a process for preparing a 2,3- or 3,4-dehydro-5-phenylmorphan compound of the formulae



wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;

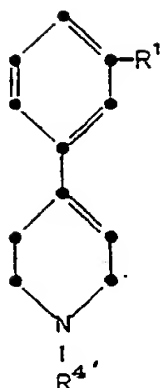
$R^{4'}$ is hydrogen or C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or $CH_2C_3-C_6$ cycloalkyl; and

B is an anion characterized by reacting a 1,2,5,6-tetrahydro-4-phenylpyridine compound of the formula

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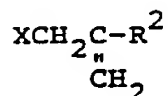
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with a propenyl alkylating agent of the formula



15 wherein:

R^1 is hydrogen, hydroxy or $\text{C}_1\text{-C}_3$ alkoxy;

R^2 is hydrogen, $\text{C}_1\text{-C}_5$ alkyl or $\text{CH}_2\text{C}_2\text{-C}_4$

alkenyl;

20

$\text{R}^{4'}$ is hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl, phenyl $\text{C}_1\text{-C}_3$ alkyl, or $\text{CH}_2\text{C}_3\text{-C}_6$ cycloalkyl; and X is a good leaving group;

in the presence of a strong base to provide a 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula

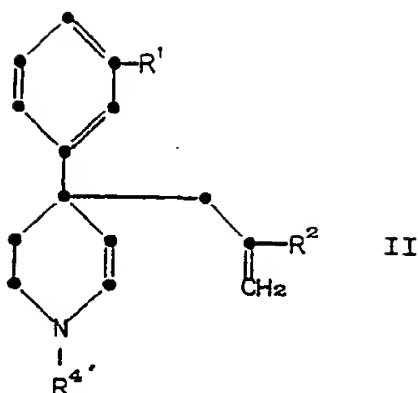
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wherein:

R^1 , R^2 and R^4 are the same as above and reacting said compound with a protonic acid of the formula HB' , in which B' is an anion B or B'' wherein the product is recovered as the salt in which B' is the anion B or as the free base of a salt in which B is exchanged for the anion B'' .

As used throughout this specification and in the appended claims, R^1 includes " C_1 - C_3 alkoxy" such as methoxy, ethoxy and n-propoxy. A preferred alkoxy group is methoxy.

R^2 and R^3 are defined to include " C_1 - C_5 alkyl" groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl and isopentyl, as well as " CH_2C_2 - C_4 alkenyl" groups such as allyl, 3-butenyl, 2-pentenyl, 2-methyl-2-butenyl and the like.

R^4 as defined herein includes " C_1 - C_{10} alkyl" groups such as methyl, ethyl, n-pentyl, isohexyl, 2-methylheptyl, 1,1-dimethylheptyl, 2-ethyloctyl, n-nonyl, n-decyl, and related alkyl groups. R^4 also includes

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"C₁-C₃ phenylalkyl groups such as benzyl, 2-phenethyl and 3-phenylpropyl. The term "CH₂C₂-C₉ alkenyl" refers to groups such as allyl, 3-butenyl, 3-pentenyl, 4-hexenyl, 2,3-dimethyl-2-pentenyl, 3-octenyl, 5-decenyl and the like. R⁴ additionally includes "CH₂C₃-C₆ cycloalkyl" groups such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl. Cyclopropylmethyl is a preferred cycloalkyl substituent.

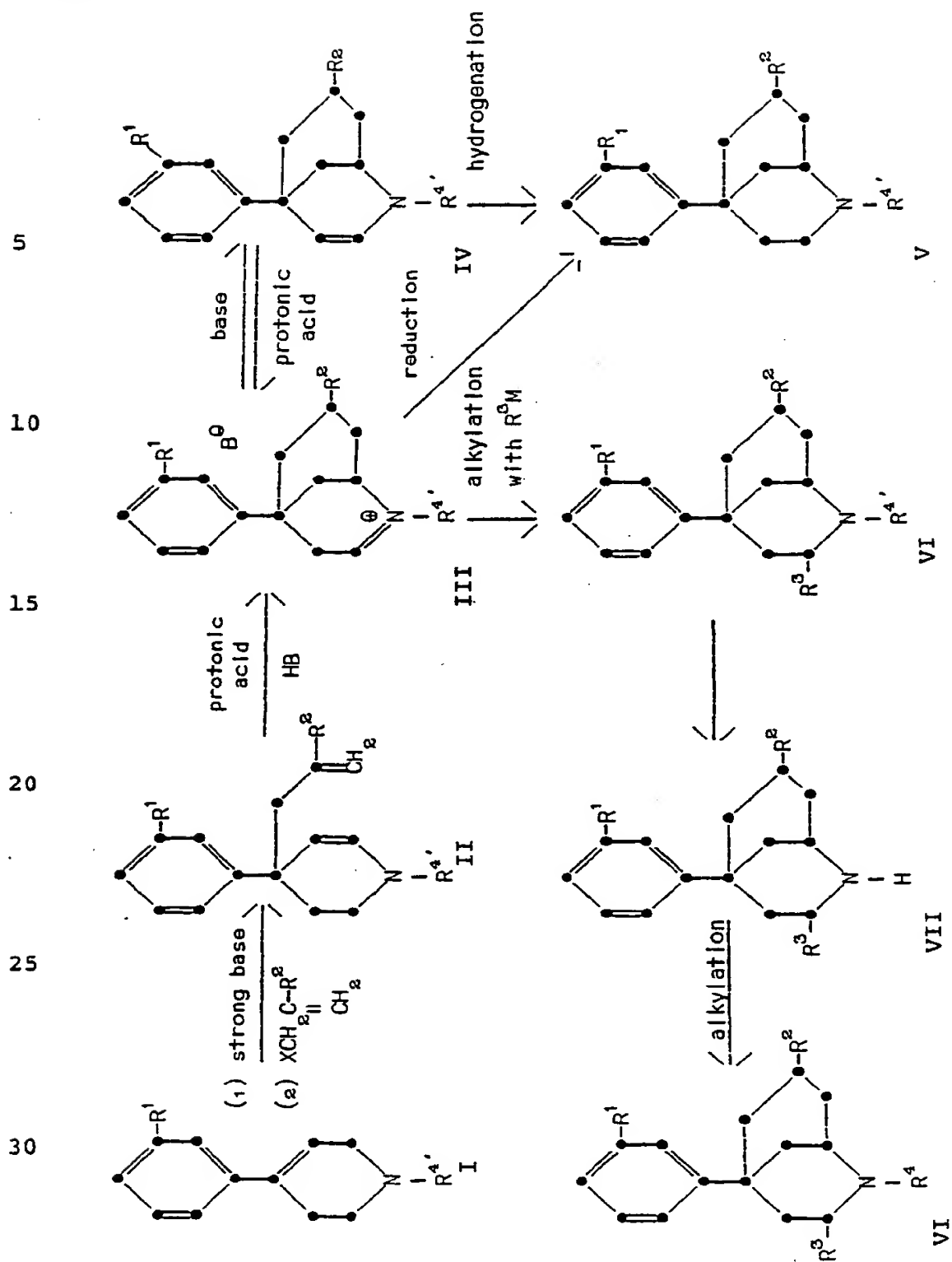
The phenylmorphane compounds provided by this invention are prepared by reacting a 1-alkyl-4-phenyl-1,2,5,6-tetrahydropyridine of Formula I with a strong base such as butyl lithium or phenyl lithium and a propenyl alkylating agent such as allyl bromide to provide a 1-alkyl-4-phenyl-4-(2-propenyl)-1,4,5,6-tetrahydropyridine of Formula II. The latter compound is reacted with a protonic acid to effect ring closure with concomitant double bond migration to give a 2-alkyl-2,3-dehydro-5-phenylmorphane salt of Formula III. Reduction of the double bond of such salt affords the corresponding 3-unsubstituted phenylmorphane of Formula V, whereas alkylation of the 2,3-dehydro-5-phenylmorphane salt provides the corresponding 3-substituted-phenylmorphane of Formula VI the invention. The overall reaction is depicted in the following general scheme:

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In the above scheme, R^1 , R^2 , R^3 and $R^{4'}$ are as defined hereinbefore, X is a leaving group and B and M are ionic radicals. It should be noted that when the above reactions are carried out wherein R^1 is methoxy, R^2 and R^3 both are hydrogen and $R^{4'}$ is methyl, the compound prepared is one disclosed by Rogers et al. in J. Med. Chem. 17, 1328 (1974), and is a precursor to the potent analgesic 2-methyl-5-(3-hydroxyphenyl)morphan. The process provided herein is an improvement over the prior art processes for preparing phenylmorphans since the product is produced in over fifty percent yield whereas the prior art processes produce the product in less than ten percent overall yield.

The first step in the process of this invention is the reaction of a 4-phenyl-1,2,5,6-tetrahydropyridine of Formula I with a strong base and a propenyl alkylating agent. Strong bases commonly utilized in the reaction include lower alkyl metalides such as methyl lithium, methyl sodium, n-propyl potassium, n-butyl lithium, as well as amides such as lithium diisopropylamide, sodium amide, lithium diethylamide, and hydrides such as sodium hydride. Typical propenyl alkylating agents include allyl bromide, allyl iodide, 2-methylallyl bromide, 2-ethylallyl p-toluenesulfonate, 2-n-propylallyl azide, 2-ethenylallyl iodide, 2-(2-propenyl)allyl azide, 2-(n-pentyl)allyl bromide and the like. The alkylation of the 4-phenyl-1,2,5,6-tetrahydropyridine of Formula I is carried out by first reacting the pyridine derivative with about a 1 to 20 molar excess of a strong base in an unreactive organic

solvent such as diethyl ether, tetrahydrofuran, dioxane, dichloromethane, benzene or the like. The reaction commonly is carried out at a reduced temperature of from 10 to -60°C. The tetrahydropyridine and the strong base are simply mixed together in a suitable solvent and stirred for 10 to 20 minutes, and then the reaction mixture is added to a solution containing about an equimolar amount or an excess of the appropriate propenyl alkylating agent in a suitable unreactive solvent such as diethyl ether, dioxane, or the like. The alkylation reaction typically is complete within 10 minutes to 2 hours when carried out at a temperature of from 25 to -60°C. The product is readily isolated by simply adding water or brine to the reaction mixture, separating the organic layer and then removing the organic solvent, for instance by evaporation under reduced pressure. The product, a 1-alkyl-4-allyl (or 2-alkylallyl or 2-alkenylallyl)-4-phenyl-1,4,5,6-tetrahydropyridine of Formula II, can be further purified if desired by conventional methods such as distillation, chromatography and the like.

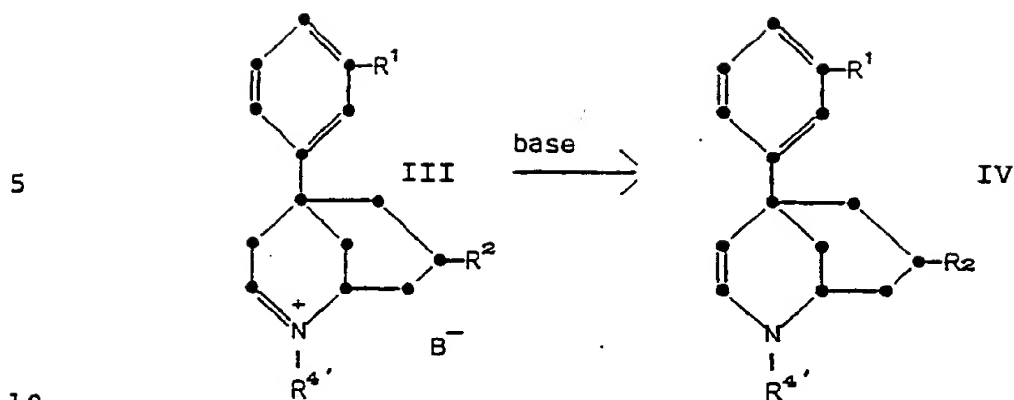
The next step in the process of this invention comprises reacting the 1-alkyl-4-allyl (or 2-alkylallyl or 2-alkenylallyl)-4-phenyl-1,4,5,6-tetrahydropyridine of Formula II with a protonic acid to effect cyclization and concomitant double bond migration to provide a 2-alkyl-2,3-dehydro-5-phenylmorphanium salt of Formula III. Any of a number of protonic acids can be utilized to effect the cyclization and double bond migration. Commonly used acids include phosphoric acid, tetrafluoro-

boric acid, hydrochloric acid, sulfuric acid, nitric acid, para-toluenesulfonic acid, and related protonic acids. Phosphoric acid is a preferred protonic acid. The cyclization reaction generally is carried out in a solvent, typically an acidic solvent such as formic acid, acetic acid, sulfuric acid, hydrochloric acid or the like. Non-acidic solvents which can be used include dioxane, tetrahydrofuran and N,N-dimethylformamide. A preferred solvent is formic acid.

10 The allyl substituted tetrahydro pyridine typically is dissolved in an excess of protonic acid such as phosphoric acid in a suitable solvent such as formic acid. The reaction can be carried out at a temperature from 0°C. to 50°C., and routinely is carried out at 20°C. to 30°C. The cyclization routinely is complete within about 24 to about 72 hours. As noted in the above mechanistic scheme, the product from such protonic acid cyclization reaction is a salt, namely a 2-alkyl-2,3-dehydro-5-phenyl-7-(unsubstituted or substituted) morphanium salt of Formula III. Such intermediate salt can readily be isolated by simply removing the reaction solvent and recrystallizing the salt from common solvents such as ethyl acetate, ethanol, and the like. An alternative method for obtaining the salt intermediate in a purified form comprises first making the acidic reaction mixture basic, for instance by adding a base such as sodium hydroxide, potassium hydroxide, sodium ethoxide or butyl lithium, thereby converting the 2,3-dehydrophenylmorphanium salt of Formula III to a free base of Formula IV according to the following scheme:

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wherein R^1 , R^2 and $R^{4'}$ are as defined above. The 3,4-dehydrophenylmorphane free base thus formed is readily isolated by simply extracting the alkaline reaction mixture with a water immiscible solvent such as diethyl ether or chloroform, and then removing the organic solvent by evaporation. Reaction of such free base with a protonic acid converts it back again to the corresponding 2,3-dehydrophenylmorphanium salt of Formula III. Examples of typical 2-alkyl-2,3-dehydro-5-phenylmorphanium salts and 2-alkyl-3,4-dehydro-5-phenylmorphanes thus prepared include the following:

2-methyl-2,3-dehydro-5-phenylmorphanium tetrafluoroborate;

2-methyl-2,3-dehydro-5-(3-methoxyphenyl)-7-methylmorphanium bromide;

2-isopropyl-2,3-dehydro-5-(3-ethoxyphenyl)-7-ethylmorphanium perchlorate;

2-cyclopropylmethyl-2,3-dehydro-5-phenyl-7-n-pentylmorphanium acetate;

- 2-benzyl-2,3-dehydro-5-(3-methoxyphenyl)-7-
n-butylmorphanium sulfate;
2-methyl-3,4-dehydro-5-phenylmorphane;
2-ethyl-3,4-dehydro-5-(3-methoxyphenyl)-
5 morphane;
2-isopropyl-3,4-dehydro-5-(3-ethoxyphenyl)-
morphane;
2-cyclopropylmethyl-3,4-dehydro-5-(3-
hydroxyphenyl)morphane;
10 2-benzyl-3,4-dehydro-5-phenyl-7-methyl-
morphane;
2-methyl-3,4-dehydro-5-(3-methoxyphenyl)-
7-ethylmorphane;
2-n-heptyl-3,4-dehydro-5-phenyl-7-n-
15 pentylmorphane; and
2-(2-phenylethyl)-3,4-dehydro-5-(3-
methoxyphenyl)-7-(3-butenyl)morphane.

The phenylmorphans of this invention which
are substituted at the 3-position with an alkyl or
20 alkenyl group are prepared by alkylation of a 2-sub-
stituted-2,3-dehydro-5-phenylmorphanium salt. Alkylat-
ing agents utilized in the reaction are defined by
the formula R^3M wherein R^3 is C_1-C_5 alkyl or $CH_2C_2-C_4$
alkenyl and M is a cationic radical. Commonly
25 utilized alkylating agents include alkali metal alkyl
or alkenyl metalides such as methyl lithium, ethyl
sodium, n-butyl lithium, isopentyl potassium, 2-
propenyl lithium, 3-butenyl sodium and related alkyl
or alkenyl metalides. Additional alkylating agents
30 which can be used are Grignard reagents of the formula

R^3 Mg halide, such as methyl magnesium bromide and n-propyl magnesium iodide, as well as dialkyl cuprates such as diethyl cuprate and diallyl cuprate.

The alkylation reaction preferably is
5 carried out by combining the appropriate 2-substituted-2,3-dehydro-5-phenyl-(7-substituted or unsubstituted)-morphanium salt of Formula III with an equimolar amount or excess of alkylating or alkenylating agent in an unreactive organic solvent such as diethyl ether,
10 diisopropyl ether, dioxane, tetrahydrofuran or the like. The reaction generally is complete within two to ten hours when carried out at 20 to 40°C. The product, a 2,3-disubstituted-5-phenyl-(7-substituted or unsubstituted)morphan of Formula VI, is isolated by diluting
15 the reaction mixture with aqueous ammonium chloride and then washing the organic layer several times with water. Separation of the organic layer and evaporation of the solvent therefrom then provides the product as a solid or an oil. Further purification can be accomplished
20 if desired by routine methods such as column chromatography, crystallization, salt formation and the like.

The phenylmorphans of this invention which are unsubstituted at the 3-position can be prepared by reduction of a 2,3-dehydro-5-phenylmorphanium salt of
25 Formula III. For example, a salt such as 2-benzyl-2,3-dehydro-5-(3-ethoxyphenyl)-7-ethylmorphanium tetrafluoroborate can be reacted with about an equimolar quantity or excess of a reducing agent such as sodium borohydride or lithium aluminum hydride to provide
30 the corresponding saturated phenylmorphan, i.e.

2-benzyl-5-(3-ethoxyphenyl)-7-ethylmorphan.

Such 3-unsubstituted phenylmorphans can alternatively be prepared by catalytic hydrogenation of the aforementioned 3,4-dehydro-5-phenylmorphans. For example, a compound such as 2-cyclopropylmethyl-3,4-dehydro-5-(3-hydroxyphenyl)-7-isobutylmorphan can be hydrogenated in the presence of a suitable catalyst to provide 2-cyclopropylmethyl-5-(3-hydroxyphenyl)-7-isobutylmorphan. The catalytic hydrogenation reactions typically are carried out in organic solvents such as methanol or ethanol, and with common catalysts such as palladium on carbon, platinum, Raney nickel and the like. When the reaction is carried out at 20 to 50°C. with a hydrogen pressure of 30 to 80 psi, the reduction is substantially complete after one-half to twenty-four hours. The reduced product is readily isolated by simply filtering the reaction mixture and then removing the reaction solvent. The phenylmorphans thus formed can be further purified if desired by routine methods such as crystallization, chromatography and salt formation.

Certain of the phenylmorphans provided by this invention are useful both as analgesics and as intermediates leading to other phenylmorphans. For example, the 2-methyl-phenylmorphans of the invention can be demethylated to provide the corresponding 2-unsubstituted phenylmorphans, which then can be alkylated with any R⁴ alkylating agent to give the other compounds of the invention. Such demethylation is accomplished by reacting the 2-methyl-phenylmorphans with a haloform-

mate to provide a carbamate, which is then converted to the demethylated product upon reaction with a base such as sodium or potassium hydroxide. The demethylation reaction thus contemplated is described in detail in
5 U.S. Patent No. 4,081,450.

The 2-benzyl-5-phenylmorphans of the invention also can be converted to 2-unsubstituted phenylmorphans which can subsequently be alkylated as desired. Debenzylation is accomplished by catalytic
10 hydrogenation in the presence of a suitable catalyst such as platinum or palladium. For example, a phenylmorphane such as 2-benzyl-3-ethyl-5-(3-methoxyphenyl)-7-methylmorphane can be hydrogenated in the presence of palladium on carbon in ethanol for two hours at 50°C.
15 under a hydrogen atmosphere of 60 psi to effect debenzoylation and thus afford 3-ethyl-5-(3-methoxyphenyl)-7-methylmorphane.

The 2-unsubstituted phenylmorphans of the invention are particularly useful as intermediates in
20 the synthesis of other compounds of the invention. Normal alkylation with a C_1 - C_{10} alkyl, CH_2C_2 - C_9 alkenyl, C_1 - C_3 alkylphenyl or CH_2C_3 - C_6 cycloalkyl alkylating agent affords the analgesically active phenylmorphans of this invention. For example, an
25 alkylating agent such as allyl bromide can be reacted with a phenylmorphane such as 3-ethyl-5-phenyl-7-methylmorphane to provide 2-allyl-3-ethyl-5-phenyl-7-methylmorphane. Such alkylation reactions generally are carried out in a solvent such as dioxane or tetra-
30 hydrofuran and usually in the presence of a base such

as triethylamine or pyridine to act as an acid scavenger. The reactions normally are complete after two to four hours when carried out at 30 to 100°C. The alkylated product is readily recovered by adding the reaction
5 mixture to water and then extracting the aqueous mixture with a solvent such as diethyl ether, and then evaporating the organic solvent. The product thus formed can be purified by crystallization, chromatography, salt formation and the like.

10 The phenylmorphans compounds of this invention which have a hydroxyl substituent in the phenyl 3-position (i.e. R^1 is hydroxy) are preferably prepared from the corresponding 3-methoxyphenylmorphans by cleavage of the methyl ether moiety. Such cleavage generally is
15 accomplished by reaction of a 3-methoxyphenylmorphans with acids such as hydrobromic acid and acetic acid or boron tribromide. For instance, a phenylmorphans such as 2-benzyl-3,7-diethyl-5-(3-methoxyphenyl)morphans can be dissolved in a mixture of hydrobromic acid and
20 acetic acid and heated at reflux for two to twenty hours. The reaction mixture next is made alkaline and the product is extracted into a solvent such as diethyl ether to provide, after removal of the solvent, the corresponding 3-hydroxyphenylmorphans derivative, namely
25 2-benzyl-3,7-diethyl-5-(3-hydroxyphenyl)morphans.

The phenylmorphans contemplated herein are basic in nature by virtue of the indocyclic amino group located in the 2-position. Because of such basic nature, the compounds readily form acid addition salts
30 with any of a number of organic and inorganic acids.

The pharmaceutically acceptable acid addition salts so formed are provided as an additional aspect of this invention. Such salts are those which are substantially non-toxic and can be administered to animals, including humans, for the relief of pain. The salts provided by this invention are prepared by reacting a phenylmorphane with any of a number of organic acids such as acetic acid, succinic acid, maleic acid, citric acid, p-toluenesulfonic acid, benzoic acid, as well as with any of a number of inorganic acids, including hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and related acids. The pharmaceutically acceptable acid addition salts are generally highly crystalline and lend themselves to convenient purification by recrystallization from common solvents such as ethanol, water, acetone and the like.

The following listing of compounds is illustrative of the phenylmorphans provided by this invention:

2,3-dimethyl-5-(3-hydroxyphenyl)-7-ethylmorphane;
2-(2-phenylethyl)-3,7-dimethyl-5-(3-methoxyphenyl)morphane;
2-allyl-3-ethyl-5-phenylmorphane;
2-cyclobutylmethyl-3-allyl-5-(3-methoxyphenyl)-7-ethylmorphane;
2-cyclohexylmethyl-5-phenyl-7-methylmorphane;
2-(3-hexenyl)-3,7-diisopropyl-5-(3-n-propoxyphenyl)morphane;
2-(3-phenylpropyl)-3-methyl-5-(3-ethoxyphenyl)morphane;

- 2-n-octyl-3,7-dimethyl-5-phenylmorphane;
2-(3-ethylhexyl)-3-(2-butenyl)-5-(3-hydroxy-phenyl)-7-ethylmorphane;
2-benzyl-3,7-di-n-propyl-5-(3-hydroxyphenyl)-
5 morphane;
2-(2,3-dimethylheptyl)-3-ethyl-5-phenyl-7-methylmorphane;
2-(2-phenylethyl)-3,7-dimethyl-5-(3-hydroxy-phenyl)morphane;
10 2-methyl-3,7-diethyl-5-phenylmorphanium bromide;
2,3,7-triethyl-5-(3-methoxyphenyl)morphanium chloride;
2-n-butyl-3-methyl-5-(3-hydroxyphenyl)morphanium
15 acetate;
2-isopentyl-3-ethyl-5-(3-ethoxyphenyl)morphanium phosphate;
2-cyclopropylmethyl-3-methyl-5-phenyl-7-ethylmorphanium sulfate;
20 2-methyl-3-n-propyl-5-phenyl-7-(3-butenyl)-morphanium formate;
2,7-dimethyl-3-(2-pentenyl)-5-(3-methoxyphenyl)morphanium benzoate;
2-benzyl-3,7-diethyl-5-phenylmorphanium
25 succinate;
2-isopropyl-3,7-dimethyl-5-(3-hydroxyphenyl)-morphanium *p*-toluenesulfonate;
2-allyl-3-(3-pentenyl)-5-(3-n-propoxyphenyl)-7-(2-butenyl)morphanium fumarate; and related compounds.

The phenylmorphane derivatives provided by this invention are useful as analgesics in the treatment of pain in animals suffering from pain and in need of treatment. The compounds have demonstrated their pain-relieving capacity in standard biological evaluations designed to measure analgesic activity. One such test is the rat-tail jerk assay. In this test, a light beam or heat source is applied to the tail of a rat. The pain threshold of the animal is measured by the latency of the rat to remove its tail from the pain source. Column 2 in the following table presents the effective subcutaneous dose in mg/kg of a number of the compounds of this invention which causes a two second delay (ED_2 sec) in tail removal compared to the control animals receiving no drug.

In another test designed to show analgesic activity, mice are given an intraperitoneal injection of acetic acid which causes the animals to writh. An effective analgesic is one that reduces the writhings. Column 3 of the following table presents the effective subcutaneous and oral doses in mg/kg of a compound of this invention required to reduce the writhing in test animals by fifty percent (ED_{50}).

25

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Compound administered	Table I		Column III	
	Column I	Column II	Mouse writhing	
		Rat tail jerk subcutaneous injection mg./kg ED ₂ seconds	s.c. mg/kg ED ₅₀	oral mg/kg ED ₅₀
2-methyl-5-(3-methoxyphenyl)- morphane		10.0	9.6	27.5
2-methyl-5-(3-hydroxyphenyl)- morphane		1.0	1.3	29.0
2,7-dimethyl-5-(3-methoxyphenyl)- morphane		10.0	3.5	28.5
2,7-dimethyl-5-(3-hydroxyphenyl)- morphane		0.5	0.72	28.5
2,3-dimethyl-5-(3-methoxyphenyl)- morphane		15.0	13.0	17.0
2,3-dimethyl-5-(3-hydroxyphenyl)- morphane		2.0	2.0	23.0
2,3,7-trimethyl-5-(3-methoxy- phenyl)morphane		20.0	7.8	22.0
2,3,7-trimethyl-5-(3-hydroxy- phenyl)morphane		0.5	0.66	14.0

The phenylmorphans of this invention can be administered to humans suffering from pain and in need of relief. The compounds are effective as analgesics when administered orally or parenterally. The invention accordingly provides an analgesic method which comprises administering to a subject suffering from pain and in need of treatment an analgesically effective dose of a phenylmorphane defined by the above general formula. The compounds preferably are administered orally in the form of pharmaceutically acceptable acid addition salts. The dosage required to effect analgesia will vary somewhat depending upon the route of administration, the severity of the pain to be alleviated, as well as the particular analgesic agent selected to be administered. A typical oral dose will range from 0.5 to 25 mg/kg. The compounds can also be administered parenterally via the intramuscular, intravenous or subcutaneous routes. Typical parenteral doses will range from 0.1 mg/kg to 20 mg/kg. In severe cases of pain, the phenylmorphane may be administered via the intramuscular or intravenous routes, while maintenance therapy may be conveniently accomplished by oral dosing.

A further embodiment of this invention are pharmaceutical formulations comprising an analgesically effective amount of a phenylmorphane having the above general formula in combination with any of a number of suitable diluents, excipients, carriers and the like. The formulations generally will contain from 5 to 50 percent by weight of active ingredient. Commonly used diluents and carriers include lactose, sucrose, starch

powder, talc, magnesium stearate, magnesium oxide, calcium sulfate, acacia powder, gelatin, sodium alginate, sodium benzoate, stearic acid, and related adjuvants routinely used in formulation of pharmaceuticals. The phenylmorphans of this invention can be formulated as tablets, capsules, buccal seals, lozenges, and the like for oral administration. The compounds are conveniently formulated in aqueous saline or dextrose to constitute an injectable liquid solution for parenteral administration via the intravenous or intramuscular routes. Alternatively, the phenylmorphans can be dissolved in a suitable solvent such as water or ethanol and placed in a vial and lyophilized to provide a dry powder that is ready for reconstitution by the addition of a suitable amount of water, saline or the like. If desired, the formulations of this invention can contain additional analgesic agents such as propoxyphene hydrochloride or the like.

The following detailed examples are provided to illustrate various specific aspects of the invention.

Example 1

1-Methyl-4-allyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine

A solution of 74 ml. of 1.6 M n-butyl lithium was added dropwise to a cold (0°C.) stirred solution of 24.36 g. of 1-methyl-4-(3-methoxyphenyl)-1,2,5,6-tetrahydropyridine in 300 ml. of tetrahydrofuran. The reaction mixture was stirred for 10 minutes at 0°C. and then added dropwise over thirty minutes to a stirred cold

(-50°C.) solution of allyl bromide in 250 ml. of diethyl ether. The reaction mixture was warmed to 0°C. and then diluted with 500 ml. of aqueous sodium chloride solution. The organic layer was separated, diluted with
5 an additional 2 liters of diethyl ether, washed with water and dried. Removal of the solvent by evaporation under reduced pressure provided 33 g. of the crude product as an oil. The oil was distilled twice to provide 17.91 g. of 1-methyl-4-allyl-4-(3-methoxyphenyl)-
10 1,4,5,6-tetrahydropyridine. B.P. 120-123°C. at 0.1 torr.

Analysis calc. for $C_{16}H_{21}NO$

Theory: C, 78.97; H, 8.70; N, 5.76.

Found: C, 78.72; H, 8.55; N, 5.48.

Example 2

15

2-Methyl-3,4-dehydro-5-(3-methoxyphenyl)morphan.

A solution of 1.0 g. of 1-methyl-4-allyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine dissolved in 2.5 ml. of 85.8 percent aqueous phosphoric acid and
20 2.5 ml. of formic acid was stirred for sixty-six hours at 24°C. under a nitrogen atmosphere. The reaction mixture then was diluted with 150 ml. of ice water and made alkaline by the addition of 50 percent aqueous sodium hydroxide. The product was extracted from the
25 alkaline solution into diethyl ether. The ethereal extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 950 mg. of 2-methyl-3,4-dehydro-5-(3-methoxyphenyl)morphan.

30

Mass spec. Theory 243, Found 243.

Example 3

2-Methyl-5-(3-methoxyphenyl)morphan

A solution of 4.0 g. of 2-methyl-3,4-dehydro-5-(3-methoxyphenyl)morphan in 150 ml. of ethanol containing 1.5 g. of five percent palladium on carbon was stirred for eighteen hours at 24°C. under a hydrogen pressure of 60 psi. The reaction mixture then was filtered and the solvent was evaporated from the filtrate to provide 3.72 g. of 2-methyl-5-(3-methoxyphenyl)morphan.

The product thus obtained was dissolved in 60 ml. of isopropanol and the solution was saturated with hydrogen bromide to form 3.22 g. of a white precipitate. The precipitated salt was recrystallized from 20 ml. of diisopropyl ether and 40 ml. of isopropanol to provide 1.0 g. of 2-methyl-5-(3-methoxyphenyl)-morphanium bromide. M.P. 152.5-154°C.

Analysis calc. for $C_{16}H_{24}BrNO$

Theory: C, 58.90; H, 7.41; N, 4.29.

Found: C, 59.19; H, 7.13; N, 4.04.

Example 4

2-Methyl-5-(3-hydroxyphenyl)morphan

A solution of 2.22 g. of 2-methyl-5-(3-methoxyphenyl)morphanium bromide dissolved in a mixture of 30 ml. glacial acetic acid and 30 ml. of 48 percent aqueous hydrobromic acid was heated at reflux for sixteen hours. The reaction mixture then was cooled to room temperature, diluted with 100 ml. of water and made alkaline to pH 9.5 with sodium hydroxide solution. The

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alkaline solution was extracted with diethyl ether, and the ethereal extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure provided 1.29 g. of the product as a
5 syrup. The syrup was dissolved in 25 ml. of diisopropyl ether and 125 ml. of isopropanol, and the solution was saturated with hydrogen bromide. The precipitate which formed was collected by filtration and dried to afford 1.0 g. of 2-methyl-5-(3-hydroxyphenyl)morphanium
10 bromide. M.P. 207-208.5°C.

Analysis calc. for $C_{15}H_{22}BrNO$

Theory: C, 57.70; H, 7.10; N, 4.49.

Found: C, 57.45; H, 6.87; N, 4.25.

Example 5

15 1-Methyl-4-(3-methoxyphenyl)-4-(2-methylallyl)-1,4,5,6-tetrahydropyridine

A solution of 74 ml. of 1.6 molar *n*-butyl lithium in tetrahydrofuran was added dropwise to a cold
20 stirred solution of 24.36 g. of 1-methyl-4-(3-methoxyphenyl)-1,2,5,6-tetrahydropyridine in 300 ml. of tetrahydrofuran. After the addition was complete and the reaction mixture had been stirred at 0°C. for ten minutes, the mixture was added dropwise over thirty minutes
25 to a stirred cold (-50°C.) solution of 10.86 g. of 3-chloro-2-methylpropene (methallyl chloride) in 250 ml. of diethyl ether. The reaction mixture was stirred and allowed to warm slowly to 0°C., at which time the reaction mixture was diluted by the dropwise
30 addition of 500 ml. of saturated aqueous sodium chloride solution. The organic layer next was separated, diluted

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with 2 liters of fresh diethyl ether, washed with fresh water and dried. Removal of the solvent by evaporation under reduced pressure then provided 33.43 g. of an oil, which after distillation gave 20.97 g. of 1-methyl-4-(3-methoxyphenyl)-4-(2-methylallyl)-1,4,5,6-tetrahydro-pyridine. B.P. 138-141°C. at 0.1 torr. Mass spec. Theory: 257; Found M^+ 257.

Example 6

10 2,7-Dimethyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate

Twenty grams of 1-methyl-4-(3-methoxyphenyl)-4-(2-methylallyl)-1,4,5,6,-tetrahydropyridine were dissolved in 50 ml. of 85.8% aqueous phosphoric acid containing 50 ml. of formic acid. The reaction mixture was stirred for forty-eight hours at ambient temperature, and then diluted by the addition of 300 ml. of ice water. Fifty percent aqueous sodium hydroxide was added to the aqueous reaction mixture to pH 11, and then the product was extracted therefrom into diethyl ether. The ethereal extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure afforded 21 g. of crude oil, which after distillation gave 17.68 g. of 2,7-dimethyl-3,4-dehydro-5-(3-methoxyphenyl)morphan. B.P. 130-138°C. at 0.1 torr.

Excess perchloric acid was added to a solution of 12.68 g. of the compound thus prepared dissolved in diethyl ether. The precipitated salt which formed was collected and recrystallized from 200 ml. of ethanol to afford 12.82 g. of 2,7-dimethyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate. M.P. 131-133°C.

Example 7

2,7-Dimethyl-5-(3-methoxyphenyl)morphan

5 A solution containing 5 g. of 2,7-dimethyl-3,4-dehydro-5-(3-methoxyphenyl)morphan dissolved in 200 ml. of ethanol containing 5 g. of five percent palladium on carbon was stirred for twenty-four hours at about 24°C. under hydrogen at 60 psi. The reaction mixture then was filtered and the solvent was removed from the filtrate by evaporation to give 4.8 g. of an oil. The oil was then dissolved in 100 ml. of diethyl ether and the solution was saturated with hydrogen bromide to effect salt formation. The salt precipitated out of solution and was collected and recrystallized from 30 ml. of diisopropyl ether and 25 ml. of isopropanol to provide 1.78 g. of 2,7-dimethyl-5-(3-methoxyphenyl)morphanium bromide. M.P. 178-181°C.

Analysis calc. for $C_{17}H_{26}BrNO$

Theory: C, 60.00; H, 7.70; N, 4.12.

20 Found: C, 59.74; H, 7.47; N, 4.38.

Example 8

2,7-Dimethyl-5-(3-hydroxyphenyl)morphan

Following the procedure set forth in Example 4, 1.1 g. of 2,7-dimethyl-5-(3-methoxyphenyl)morphan was dissolved in a solution of 15 ml. of 48 percent hydrobromic acid and 15 ml. of glacial acetic acid, and the reaction mixture was heated at reflux for sixteen hours. Normal workup of the reaction mixture afforded 710 mg. of the product as an oil, which then was converted to its hydrobromide salt. Recrystallization of

the salt from 30 ml. of diisopropyl ether and 20 ml. of isopropanol afforded 620 mg. of 2,7-dihydroxy-5-(3-hydroxyphenyl)morphanium bromide. M.P. 239-241.5°C.

Analysis calc. for $C_{16}H_{24}BrNO$

5 Theory: C, 58.90; H, 7.41; N, 4.29.

Found: C, 59.11; H, 7.30; N, 4.50.

Example 9

2,3,7-Trimethyl-5-(3-methoxyphenyl)morphan

10 To a stirred solution of 60 ml. of 1.6 molar methyl lithium in diethyl ether at 24°C. was added portionwise over thirty minutes 6.0 g. of 2,7-dimethyl-2,3-dehydro-5-(3-methoxyphenyl)morphanium perchlorate (from Example 6). The reaction mixture was stirred at 24°C.
15 for two hours following complete addition of the salt. The reaction mixture next was diluted by the addition of 30 ml. of saturated aqueous ammonium chloride, and the organic layer then was separated, washed with water and dried. Removal of the solvent by evaporation under
20 reduced pressure afforded 4.79 g. of the product as an oil. The oil was converted to the hydrobromide salt by reaction with hydrogen bromide in diethyl ether. The salt thus formed was recrystallized from 100 ml. of diisopropyl ether and 250 ml. of isopropanol to give
25 3.18 g. of 2,3,7-trimethyl-5-(3-methoxyphenyl)morphanium bromide. M.P. 191-194°C.

Analysis calc. for $C_{18}H_{28}BrNO$

Theory: C, 61.02; H, 7.97; N, 3.95.

Found: C, 61.01; H, 7.79; N, 4.20.

Example 10

2,3,7-Trimethyl-5-(3-hydroxyphenyl)morphan

Two grams of 2,3,7-trimethyl-5-(3-methoxy-
phenyl)morphan was reacted with hydrobromic acid and
acetic acid according to the procedure set out in
Example 4 to provide 1.43 g. of the title compound as a
solid substance. The compound was purified by crystal-
lization from 50 ml. of ethyl acetate and 15 ml. of
ethanol to give 1.17 g. of 2,3,7-trimethyl-5-(3-hydroxy-
phenyl)morphan. M.P. 193°C. (dec.).

Analysis calc. for $C_{17}H_{25}NO$

Theory: C, 78.72; H, 9.71; N, 5.40.

Found: C, 78.61; H, 9.54; N, 5.20.

Example 11

2,3-Dimethyl-5-(3-methoxyphenyl)morphan

Eight grams of 2-methyl-2,3-dehydro-5-(3-
methoxyphenyl)morphanium perchlorate were reacted with
75 ml. of 1.6 molar methyl lithium in diethyl ether
according to the general procedure set out in Example 9
to give 6.33 g. of 2,3-dimethyl-5-(3-methoxyphenyl)-
morphan. B.P. 140-143°C. at 0.1 torr.

The compound thus formed was converted to its
hydrobromide salt by reaction with excess hydrogen
bromide in diethyl ether. The salt which precipitated
was collected and recrystallized twice from 25 ml. of
diisopropyl ether and 100 ml. of isopropanol to give
2.79 g. of 2,3-dimethyl-5-(3-methoxyphenyl)morphanium
bromide. M.P. 192.5-194°C.

Analysis calc. for $C_{17}H_{24}BrNO$

Theory: C, 60.00; H, 7.77; N, 4.12.

Found: C, 59.87; H, 7.50; N, 4.11.

Example 12

2,3-Dimethyl-5-(3-hydroxyphenyl)morphan

Two grams of 2,3-dimethyl-5-(3-methoxyphenyl)-
morphanium bromide were reacted with 25 ml. of 48 per-
cent hydrobromic acid and 25 ml. of acetic acid accord-
ing to the procedure of Example 4 to give, after puri-
fication by salt formation and recrystallization,
900 mg. of 2,3-dimethyl-5-(3-hydroxyphenyl)morphanium
bromide. M.P. 237-239°C.

Analysis calc. for $C_{16}H_{24}BrNO$

Theory: C, 58.90; H, 7.41; N, 4.29.

Found: C, 58.69; H, 7.21; N, 4.49.

Example 13

3,7-Dimethyl-5-(3-methoxyphenyl)morphan

To a solution of 2,3,7-trimethyl-5-(3-methoxy-
phenyl)morphan in dichloromethane is added a solution of
phenyl chloroformate in dichloromethane. The reaction
mixture is stirred for several hours at ambient tempera-
ture, and then the solvent is removed by evaporation.
The residue is made alkaline by the addition of sodium
hydroxide, and the alkaline solution is heated for
several hours. After cooling to room temperature, the
alkaline reaction mixture is extracted several times
with diethyl ether. The ethereal extracts are combined,
washed with water and dried. Evaporation of the solvent
affords 3,7-dimethyl-5-(3-methoxyphenyl)morphan.

Example 14

2-Cyclopropylmethyl-3,7-dimethyl-5-(3-methoxyphenyl)-
morphan

5 A solution of cyclopropylmethyl bromide in
tetrahydrofuran containing 3,7-dimethyl-5-(3-methoxy-
phenyl)morphan and triethylamine is heated for several
hours. The reaction mixture is then washed with water,
and the organic solvent is next removed by evaporation
under reduced pressure to provide 2-cyclopropylmethyl-
10 3,7-dimethyl-5-(3-methoxyphenyl)morphan.

Example 15

2-Benzyl-5-phenyl-7-ethylmorphan

15 A solution of 1-benzyl-4-phenyl-1,2,5,6-
tetrahydropyridine in tetrahydrofuran containing n-
butyl lithium is added to a solution of 3-chloro-
2-ethylpropene in tetrahydrofuran. The reaction is
carried out according to the procedure of Example 1 to
give 1-benzyl-4-phenyl-4-(2-ethylallyl)-1,4,5,6-tetra-
20 hydropyridine. The latter compound is reacted with
phosphoric acid and formic acid to give, after treat-
ment with sodium hydroxide, 2-benzyl-3,4-dehydro-5-
phenyl-7-ethylmorphan. Catalytic hydrogenation of the
latter compound provides 2-benzyl-5-phenyl-7-ethyl-
25 morphan.

Example 16

2-Allyl-3-isopropyl-5-phenyl-7-ethylmorphan

30 A solution of 2-benzyl-3,4-dehydro-5-phenyl-
7-ethylmorphan in diethyl ether is added to a stirred
ethereal solution of isopropyl lithium according to

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the method of Example 9 to give 2-benzyl-3-isopropyl-5-phenyl-7-ethylmorphan. Catalytic hydrogenation of the latter compound effects debenzylation to provide 3-isopropyl-5-phenyl-7-ethylmorphan. Allyl bromide is
5 reacted with the latter compound to effect N-alkylation to provide 2-allyl-3-isopropyl-5-phenyl-7-ethylmorphan.

Example 17

The following ingredients are combined and
10 molded into tablets for convenient oral administration to a subject suffering from pain and in need of treatment.

15	2-cyclopropylmethyl-3,7-dimethyl-5-(3-hydroxy-phenyl)morphanium chloride	1000 mg.
	dextrose	3500 mg.
	starch powder	<u>500 mg.</u>
		5000 mg.

The above formulation is compressed into 25 tablets
20 each containing 40 mg. of active ingredient. Such tablets are administered to a person needing analgesic treatment at the rate of from 1 to about 4 tablets per day.

25

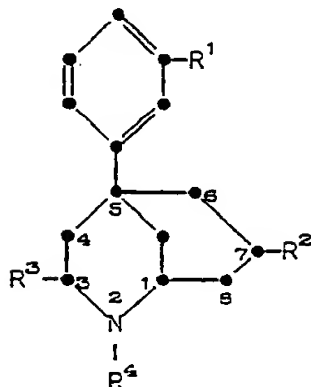
30

CLAIMS

1. A 5-phenylmorphane compound having the formula

5

10



VI

wherein:

15

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl; except that R^2 and R^3 both are not hydrogen;

20

R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, $CH_2C_2-C_9$ alkenyl, or $CH_2C_3-C_6$ cycloalkyl; and the pharmaceutically acceptable acid addition salts thereof.

2. A 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula

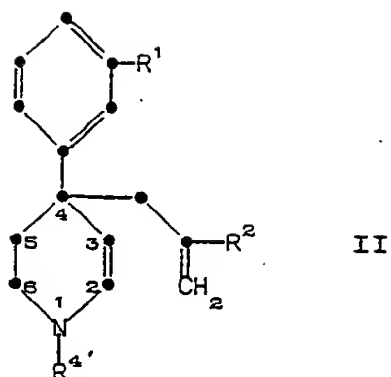
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5



10

wherein:

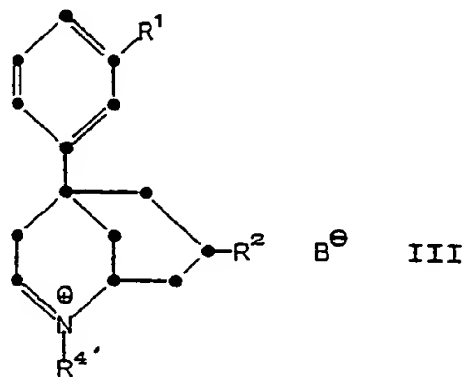
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl; and

15 $R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl.

3. A 2,3-dehydro-5-phenylmorphane compound of the formula

20



25

wherein:

30 R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

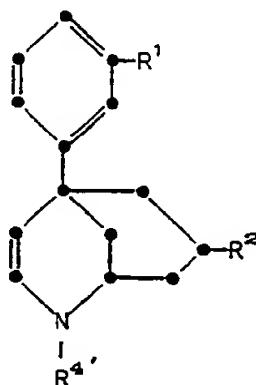
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R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl; and
 B^\ominus is an anion.

4. A 3,4-dehydro-5-phenylmorphane compound of the formula



IV

wherein:

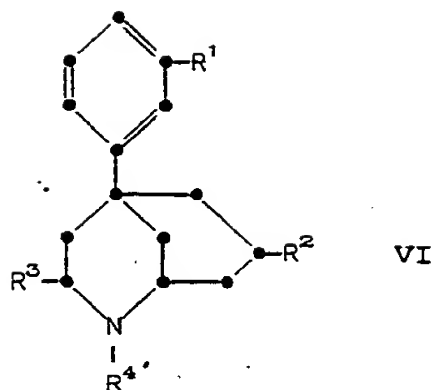
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl; and

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or $CH_2C_3-C_6$ cycloalkyl.

5. A process of preparing a 3-substituted-5-phenylmorphane compound having the formula

5

10



wherein:

- R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$
 15 alkenyl;
 R^3 is C_1-C_5 alkyl or $C_2C_2-C_4$ alkenyl;
 $R^{4'}$ is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or
 $CH_2C_3-C_6$ cycloalkyl; and
 20 the pharmaceutically acceptable acid addition
 salts thereof

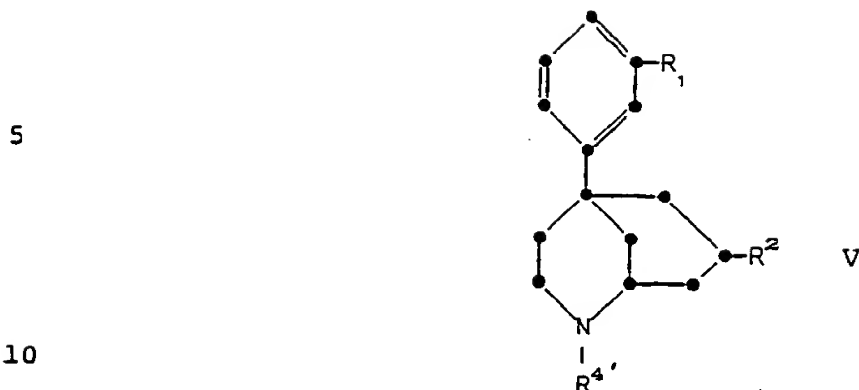
characterized by alkylating the 2,3-dehydro-
 5-phenylmorphanium salt of formula III of claim 12
 wherein R^1 , R^2 and $R^{4'}$ are as above with the compound
 R^3M where R^3 is as above and M is a cationic radical
 25 and recovering as the free base or the pharmaceutically
 acceptable acid addition salt thereof.

6. A process of preparing a 7-substituted-
 5-phenylmorphane compound having the formula

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wherein:

- 15
- R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 - R^2 is C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;
 - R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or $CH_2C_3-C_6$ cycloalkyl; and
- the pharmaceutically acceptable acid addition salts thereof

20

characterized by reducing the 2,3 dehydro-5-phenylmorphanium salt of formula III of claim 12 wherein R_1 , R_2 and $R^{4'}$ are as above with a reducing agent and recovering as the free base or the pharmaceutically acid addition salt thereof.

25

7. A process of preparing a 7-substituted-5-phenylmorphane compound having the formula V of claim 6 wherein:

- 30
- R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 - R^2 is C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl;
 - R^4 is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl; and

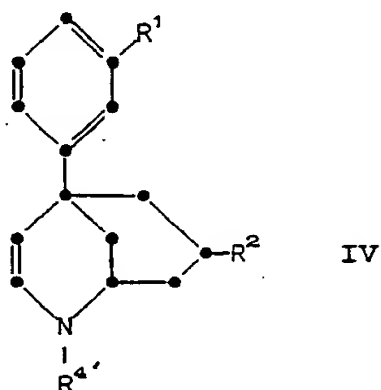
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the pharmaceutically acceptable acid addition salts thereof characterized by hydrogenating a 3,4-dehydro-5-phenylmorphan compound of the formula

5

10



15 wherein R^1 , R^2 and $R^{4'}$ are as above and recovering as the free base or as the pharmaceutically acceptable acid addition salt thereof.

20 8. A process for preparing a 2,3,7-substituted-5-phenylmorphan compound of formula VI of claim 1 wherein:

25 R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;
 R^2 and R^3 independently are hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$ alkenyl; except that R^2 and R^3 both are not hydrogen;

R^4 is C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, $CH_2C_2-C_9$ alkenyl, or $CH_2C_3-C_6$ cycloalkyl; and

the pharmaceutically acceptable acid addition salts thereof

30 characterized by reacting a 3,7-substituted-

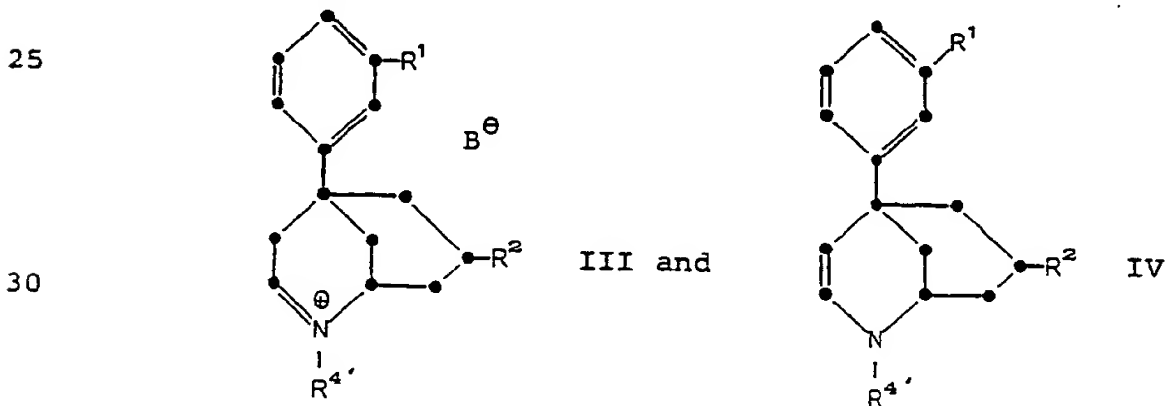
5-phenyl-morphan of formula VI wherein R^1 , R^2 and R^3 are as above and R^4 is hydrogen with an alkylating or alkenylating agent wherein R^4 is as above other than hydrogen and recovering the free base or the pharmaceutically acceptable acid salt thereof.

9. A process for preparing a 5-(3-hydroxy phenyl)morphan compound of formula VI of claim 1 wherein:

- R^1 is hydroxy;
 R^2 and R^3 independently are hydrogen, C_1 - C_5 alkyl or CH_2C_2 - C_4 alkenyl; except that R^2 and R^3 both are not hydrogen;
 R^4 is hydrogen, C_1 - C_{10} alkyl, phenyl, C_1 - C_3 alkyl, CH_2C_2 - C_9 alkenyl, or CH_2C_3 - C_6 cycloalkyl; and
the pharmaceutically acceptable acid addition salts thereof

characterized by reacting a 5-(3-methoxy phenyl)morphan with an acid such as hydrobromic acid and acetic acid or boron tribromide followed by recovery of the free base or pharmaceutically acceptable acid addition salt thereof.

10. A process for preparing a 2,3- or 3,4-dehydro-5-phenylmorphan compound of the formulae



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wherein:

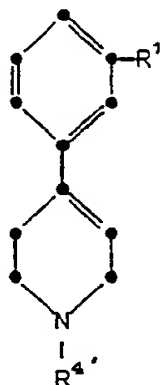
R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$

alkenyl;

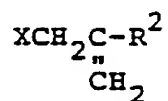
$R^{4'}$ is hydrogen or C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl or $CH_2C_3-C_6$ cycloalkyl; and

B is an anion characterized by reacting a 1,2,5,6-tetrahydro-4-phenylpyridine compound of the formula



I

with a propenyl alkylating agent of the formula



wherein:

R^1 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R^2 is hydrogen, C_1-C_5 alkyl or $CH_2C_2-C_4$

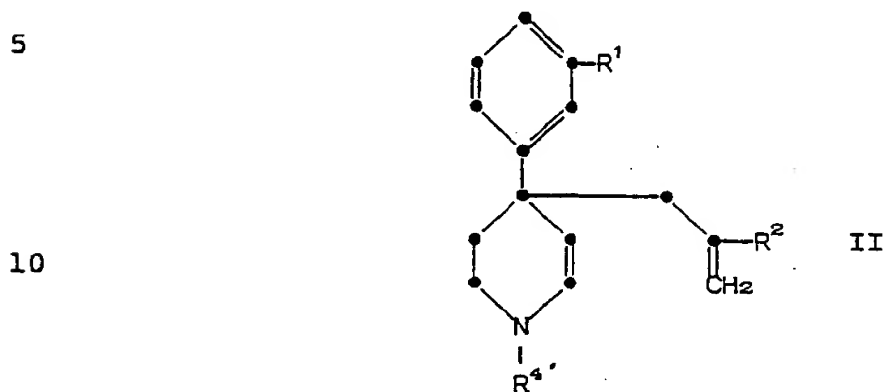
alkenyl;

$R^{4'}$ is hydrogen, C_1-C_{10} alkyl, phenyl C_1-C_3 alkyl, or $CH_2C_3-C_6$ cycloalkyl; and X is a good leaving group;

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in the presence of a strong base to provide a 1,4,5,6-tetrahydro-4-phenyl-4-(2-propenyl)-pyridine compound of the formula



wherein:

15 R^1 , R^2 and $R^{4'}$ are the same as above and reacting said compound with a protonic acid of the formula HB' , in which B' is an anion B or B'' wherein the product is recovered as the salt in which B' is the anion B or as the free base of a salt in which B is

20 exchanged for the anion B'' .

11. A pharmaceutical formulation useful in the treatment of pain comprising an analgesically effective amount of a 5-phenylmorphane compound of formula VI according to claim 1 in combination with a

25 suitable pharmaceutical carrier thereof.

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(12) **EUROPEAN PATENT APPLICATION**

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A 61 K 31/435
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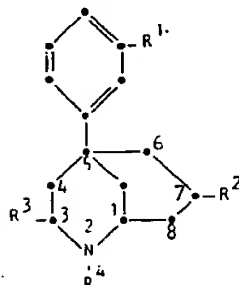
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(54) Phenylmorphans, processes for their preparation, pharmaceutical compositions containing them, and 4-phenyl-tetrahydro-pyridines.

(57) A novel 5-phenylmorphane compound having the formula



wherein:

R¹ is hydrogen, hydroxy or C₁-C₃ alkoxy;
R² and R³ independently are hydrogen, C₁-C₈ alkyl or
CH₂C₂-C₄ alkenyl; except that R² and R³ both are not hydro-
gen;

R⁴ is hydrogen, C₁-C₁₀ alkyl, phenyl C₁-C₃ alkyl,
CH₂C₃-C₆ alkenyl, or CH₂C₃-C₆ cycloalkyl; and
the pharmaceutically acceptable acid addition salts
thereof are disclosed. These compounds are useful in the
treatment of pain.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application number
EP 80 30 0746

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<p>JOURNAL OF MEDICINAL CHEMISTRY, vol. 20, no. 2, February 1977, pages 221-228 Washington US</p> <p>M. TAKEDA et al.: "Azabicycloalkanes as Analgetics. 3.1 Structure Activity Relationships of 1-Phenyl-6-azabicyclo (3.2.1) octanes and Absolute Stereochemistry of (+)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo(3.2.1.)octane and its 7-endo-methyl derivative"</p> <p>* Whole paper, particularly page 221, right-hand column, paragraph 3 *</p> <p>--</p> <p>US - A - 4 081 450 (D.M. ZIMMERMAN)</p> <p>* Whole patent *</p> <p>--</p>	<p>1,3,4,11</p>	<p>C 07 D 221/22 A 61 K 31/435/ C 07 D 211/70</p>
	<p>US - A - 4 081 450 (D.M. ZIMMERMAN)</p> <p>* Whole patent *</p> <p>--</p>	<p>2</p>	<p>C 07 D 221/22 221/70</p>
D	<p>JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 1, January 1974, pages 133-134 Washington US</p> <p>H.H. ONG: "Phenylmorphane agonists-antagonists"</p> <p>* Whole paper *</p> <p>----</p>	<p>1,11</p>	<p>TECHNICAL FIELDS SEARCHED (Int. Cl.)</p> <p>C 07 D 221/22 221/70</p> <p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons</p>
<p><input checked="" type="checkbox"/> The present search report has been drawn up for all claims</p>			<p>B: member of the same patent family, corresponding document</p>
Place of search		Date of completion of the search	Examiner
The Hague		09-09-1980	ALLARD

EPO Form 1503.1 06.78



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

- 1) Claims 1,5-9,11: 5-phenylmorphans, processes for their preparation and their use in pharmaceuticals.
- 2) Claim 2: 4-phenyltetrahydropyridines (starting compound)
- 3) Claims 3,4,10: 5-phenyl-dehydromorphans and process for their preparation (intermediates).

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims: